

EXHIBIT D

Vaccine 1997 Jun;15(8):884-7

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ELSEVIER SCIENCE
FULL-TEXT ARTICLE**Anti-HIV env immunities elicited by nucleic acid vaccines.****Shiver JW, Davies ME, Yasutomi Y, Perry HC, Freed DC, Letvin NL, Liu MA.**

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Plasmid DNA vaccines encoding HIV-1 env were used to immunize mice and nonhuman primates. Plasmids were prepared that produced either secreted gp120 or full-length gp160. Mice immunized with gp120 DNA developed strong antigen-specific antibody responses, CD8+ cytotoxic T lymphocytes (CTL) (following in vitro restimulation with gp120-derived peptide), and showed in vitro proliferation and Th1-like cytokine secretion [gamma-interferon, interleukin (IL)-2 with little or no IL-4] by lymphocytes obtained from all lymphatic compartments tested (spleen, blood, and inguinal, iliac, and mesenteric lymph nodes). This indicated that systemic anti-gp120 cell-mediated immunity was induced by this DNA vaccine. Although similar antibody responses were observed in mice immunized by either intramuscular or intradermal routes, T cell responses were significantly stronger in mice injected intramuscularly. Rhesus monkeys immunized with both gp120 and gp160 DNAs exhibited significant CD8+ CTL responses, following in vitro restimulation of peripheral blood lymphocytes with antigen. These experiments demonstrate that DNA immunization elicits potent immune responses against HIV env in both a rodent and a nonhuman primate species.

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